

REMARKS

Applicant submits this Amendment in response to an Office Action dated January 18, 2007. Claims 1-28 are pending in the application and claim 29 has been withdrawn by the Examiner as being drawn to a non-elected invention pursuant to a restriction requirement. Upon entry of the present amendment claims 3, 12 and 13 will be canceled, without prejudice, and claims 1, 2, 4-11 and 14-28 will be pending in the application. Claim 1 is an independent claim. By amendment herein, the recitation that the ultrafine particles are nanoparticles from claim 3 has been incorporated into claim 1 and all claims dependent thereon. Also, the recitation that the polymer concentration in the solution is less than about 4mg/ml so as to minimize agglomeration of the polymer coated ultrafine particles has been incorporated from claims 12 and 13 into claim 1 and all claims dependent thereon. Accordingly, claims 3, 12 and 13 have been canceled. Additionally, claim 1, and claims dependent thereon, have been amended to clarify that in the coating method claimed the polymer is caused to precipitate from the polymer solution and coat the surface of a portion of the suspended ultrafine nanoparticles to form polymer-coated ultrafine nanoparticles. Support for this is found at page 25, lines 10-12 and page 27, line 10-12.

Also, in claim 4, the weight percent of the polymer in the coated nanoparticles has been amended to "up to about 25 weight percent." Support is found at page 54, lines 1-2; and page 54, line 19, page 55, line 6. It is submitted that no new matters have been added by these amendments.

Reconsideration of the present application in view of the foregoing amendments and accompanying remarks is respectfully requested.

Election/Restrictions

Applicant affirms the provisional election, with traverse, to prosecute claims 1-28 (Group I) herein. Accordingly, the Examiner has withdrawn from prosecution herein claim 29 (GroupII).

Claim Objections

Claim 17 has been amended as suggested by the Examiner to clarify the claim language. The objection should therefore be obviated.

Claim Rejections under 35 USC 112

Claim 4 has been amended to indicate “the polymer content” is with respect to the “polymer-coated ultrafine particles”. Claim 6 has been amended by deleting the words “said quantity of” to clarify that it is the polymer-coated particles function to provide controlled release of at least one drug, gene or bioactive agent. It is respectfully submitted the rejection for indefiniteness is thereby obviated.

Claim Rejections under 35 USC 102

The Examiner has rejected claims 1-4, 6-11, 18, 20-22, and 26-28 under 35 USC 102 (b) as being anticipated by US Patent 5,833,891 to Subramanian et al. Claims 5, 12-17, 19, and 23-25 have not been rejected under this patent. It is pointed out that claim 3 and non-rejected claims 12 and 13 have now been incorporated into claim 1 by amendment herein.

The patent discloses a process for precipitating small particles of a substance by contacting a fluid dispersion of the substance with an antisolvent at or near supercritical conditions (see, for example, claims 1-20, Examples 1-4 and the abstract). The particles are **not coated**. This is quite **different** from Applicant’s claimed method of coating nanoparticles with a

polymer comprising combining a supercritical fluid (for example, carbon dioxide or ammonia) with a polymer solution having nanoparticles (for example, a medicament) suspended in the polymer solution to cause precipitation of the polymer from the solution and coat the nanoparticles to form polymer-coated nanoparticles, wherein the polymer concentration in the solution is less than about 4 mg/ml so as to minimize agglomeration of the polymer-coated nanoparticles.

Also, the patent discloses a process for coating core particles with a desired substance by contacting a dispersion of the desired substance with a fluidized flow of the core particles created by a fluidizing gas stream of an antisolvent at or near supercritical conditions (see, for example, claims 21-46, Examples 5-8 and the abstract). In examples 5-8, core particles of 2 mm glass beads and 1.5 mm nonpareil sugar were coated with either a drug (hydrocortisone) or a polymer (RG503H). This is quite **different** from the method claimed by Applicant in several respects. First, Applicant's method does **not** utilize core particles in a fluidized gas stream to effect the coating, but instead discloses having the **nanoparticle to be coated contained as a suspension in a solution of the polymer**, when contacted by the supercritical antisolvent. Thus Applicant does not use in the claimed method core particles. Second, the '891 patent does **not** disclose or recognize the method as claimed by Applicant, of using a **polymer concentration of less than about 4 mg/ml of solution so as to minimize agglomeration effects in the polymer-coated nanoparticles**. Third, the 1.5-2 million nanometer (or 1.5-2 mm) core particle size range referred to in the patent, namely Examples 5-8, are the only examples for coating particles in the '891 patent. The particle sizes in Examples 5-8 are substantially greater than the **nanoparticle** size used in Applicant's claimed coating method. Although the patent claims directed to coating

core particles, namely claims 36 and 37, refer to coated particles in the nanometer range (0.6 um or 600 nanometers), **the patent also teaches away** from methodology for making polymer-coated nanoparticles as in Applicant's claimed method. For example, the patent indicates the following (see column 7, lines 9-31):

“A wide variety of core particles can be used in the invention but generally these should have a maximum dimension of up to about 15 mm, and more preferably up to about 1 mm. Core particles such as ...can be coated. The final coated products can range from micron-sized to several millimeters. In the case of medicaments, depending on the application, the final coatings would typically have a thickness of from about 0.1 um to 2 mm (more preferably from about 1-500um), and the coating...of the final coated product.”

Thus, the **core particle size range** is up to about 1-15 mm, or up to about 1 million to 15 million nanometers; the **additional coating thickness** on the core particles is 0.1 um to 2 mm, or 100 nanometers to 2 million nanometers. The total coated particles resulting from this patent teaching are **substantially larger** than the coated nanoparticles (i.e., particle sizes under 1 um) according to Applicant's claimed method.

In view of the foregoing remarks and amendments to the claims, it is respectfully submitted that the '891 patent does not teach the method claimed in amended claim 1 and claims dependent thereon, and that this rejection should be withdrawn.

The Examiner has rejected claims 1, 2, 5, 6, 9, 18, 21 and 28 under 35 USC 102(e) as being anticipated by the cited Bertuccio et al article. Claims 3, 4, 7, 8, 10-17, 19, 20 and 22-28

have not been rejected under this patent. It is pointed out that non-rejected claims 3, 12 and 13 have now been incorporated into claim 1 by amendment herein.

This article discloses a method for encapsulating particles of a water soluble drug held in suspension in a polymer solution by contacting the solution with compressed carbon dioxide gas at supercritical conditions. **However, the method of the article is different** in that there is no teaching as in Applicant's claimed process of coating nanoparticles **and** minimizing agglomeration of the polymer-coated nanoparticles by using a polymer concentration of less than about 4 mg/ml of solution. In view of the foregoing remarks and amendments to the claims, it is respectfully submitted that the article does not teach the method claimed in amended claim 1 and claims dependent thereon, and that this rejection should be withdrawn.

The Examiner has rejected claims 1, 3, 5-8, 10, 11, 14-17, 18 and 26 under 35 USC 102(e) as being anticipated by US Patent 6,620,351 to Gupta et al. Claims 2, 4, 9, 12, 13, 19-25, 27 and 28 have not been rejected under this patent. It is pointed out that claim 3 and non-rejected claims 12 and 13 have now been incorporated into claim 1 by amendment herein.

The patent discloses a method for making encapsulated core particles (e.g., magnetite) with a desired substance by combining on a vibrating surface an antisolvent at or near supercritical conditions with a dispersion of the substance having core particles held in suspension in the dispersion. **However, the method of the patent is different from that of Applicant in using a vibrating surface.** Also, there is no teaching in the patent as in Applicant's claimed process of coating nanoparticles **and minimizing agglomeration of the polymer-coated nanoparticles by using a polymer concentration of less than about 4 mg/ml of solution.** In view of the foregoing remarks and amendments to the claims, it is respectfully

submitted that the patent does not teach the method claimed in amended claim 1 and claims dependent thereon, and that this rejection should be withdrawn.

The Examiner has rejected claims 1, 2, 11, 12, 13, 18 and 22 under 35 USC 102(e) as being anticipated by Perrut US Patent Publication number 2003/0031784 A1. Claims 3-10, 14-17, 19-21 and 23-28 have not been rejected under this patent publication. It is pointed out that non-rejected claim 3 and claims 12 and 13 have now been incorporated into claim 1 by amendment herein.

The publication discloses a method of collecting and encapsulating with a coating agent **particles dispersed in a fluid at supercritical pressure**, and an installation for implementing said method (see publication abstract, lines 1-3). **However, the method of the publication is different** in that there is no teaching as in Applicant's claimed process of coating nanoparticles **and minimizing agglomeration of the polymer-coated nanoparticles by using a polymer concentration of less than about 4 mg/ml of solution**. Referring to the only two examples in the publication, a solution containing ethylcellulose as the coating agent in ethyl acetate as the solvent is contacted by a percolating stream of carbon dioxide gas (antisolvent) **containing the amoxicillin particles to be coated** at near supercritical conditions and the coated particles recovered. Specifically, patent Example 1, column 4, lines 6-9 of paragraph [0054] reads as follows:

“This particle-laden fluid was expanded to a pressure of 5.5 Mpa and was percolated within a solution of ethylcellulose in ethyl acetate containing 4.5% of this coating agent.” In other words, the **amoxicillin particles contained within the carbon dioxide fluid** were percolated through the ethyl acetate solution

containing ethylcellulose (i.e., coating polymer) to obtain the microcapsule particles of amoxicillin. Example 2, the only other example in the patent, presents an alternative installation for carrying out the same method as Example 1 except making it a continuous process. The publication refers to the language “...particles dispersed in a fluid at supercritical pressure..” in describing the process several times throughout the specification and claims (see, for example, claim 1, line 2; abstract, line 2; and paragraph [0026], line 5.

The method described in the publication is **different** from Applicant’s claimed method **wherein the particles to be coated are suspended in the solution containing the polymer prior to combining with the supercritical fluid as an antisolvent, and not** in the antisolvent as in the publication.

Also, in Example 1 of the publication, the polymer concentration of ethylcellulose in ethyl acetate solvent is given as 4.5 weight %. Using the density of 0.897 g/ml for ethyl acetate, the calculated concentration of ethyl cellulose in ethyl acetate is 5.017 g/ml (i.e., 4.5 divided by 0.897). This is still **not** less than about 4 g/ml to minimize agglomeration of the coated particles as set forth in Applicant’s claimed method. Moreover, the coated particles of amoxicillin obtained in Example 1 of the publication indicate a size between 2.5 -12.5 um (or 2500-12,500 nanometers), which is much larger than the nanometer coated particles of Applicant’s claimed method. Similar results are obtained in Example 2 of the publication.

In view of the foregoing remarks and amendments to the claims, it is respectfully submitted that the publication does not teach the method claimed in amended claim1 and claims dependent thereon, and that this rejection should be withdrawn.

Claim Rejections under 35 USC 103(a)

The Examiner has rejected claim 19 under 35 USC 103(a) as being obvious from the disclosure of the afore-mentioned Subramanian et al US Patent 5,833,891 in view of the teachings of US Patent 6,596,206 to Lee. The '206 patent discloses and claims a method and device for generating solid particles of a pharmaceutical agent by contacting a solution of the agent with an antisolvent (such as a supercritical fluid) while applying focused acoustic energy to the solution/antisolvent combination. The Examiner has acknowledged that the '891 patent does not teach using supercritical ammonia or a combination of supercritical fluids as the antisolvent in the SAS (supercritical antisolvent) process of encapsulation of ultrafine particles. The Examiner relies on the '206 patent teachings of using supercritical ammonia or combinations of supercritical fluids as the antisolvent, and the teaching of using acetone as the solvent in both the '206 and '891 patent to conclude it would be obvious to use supercritical ammonia or combinations of supercritical fluids in the '891 patent method to come upon Applicant's method in claim 19

Applicant strongly disagrees. Even if the teachings of both of the '891 and '206 patents are combined as put forth by the Examiner, it is submitted that each of the '891 and '206 patents teach different processes from that of Applicant's claimed method in main claim1, and claim 19 dependent thereon. Neither patent, individually or in combination, teaches or would render obvious Applicant's claimed process of coating nanoparticles **and minimizing agglomeration of the polymer-coated nanoparticles by using a polymer concentration of less than about 4 mg/ml of solution.**

In view of the foregoing remarks and amendments to the claims, it is respectfully submitted that claim 19 is not obvious and that this rejection should be withdrawn.

The Examiner has rejected claims 23-25 under 35 USC 103(a) as being obvious from the disclosure of the afore-mentioned Perrut US Patent Publication number 2003/0031784 A1 in view of the teachings of the aforementioned US Patent 6,596,206 to Lee. The Examiner acknowledges that the publication does not disclose formulating drug particles with a diluent or fill such as lactose, dextrose, cellulose and combinations thereof. The Examiner has also stated that the '206 patent teaches a SAS process for producing a formulated drug particle not specifically for coating a fine drug particle; however it would have been readily apparent to persons skilled in the art to have suspended the particles in the polymer solution before being delivered into the supercritical carbon dioxide antisolvent; and additionally obvious to one skilled in the art to use formulated drug particles consisting of fillers or diluents according to the teachings of the '206 patent in the method of the Subramanian et al '891 patent to produce polymer encapsulated drug particles in a similar SAS mass transfer process.

Applicant strongly disagrees. As discussed previously, neither the Subramanian '891 patent or the Perrut publication teach Applicant's method which utilizes a **suspension of the nanoparticles in a polymer solution** prior to contact with the antisolvent for coating the particles. The Lee '206 patent also does **not** teach the use of such particle suspension as in Applicant's claimed method, but teaches that the pharmaceutical agent is contained in a solution, and that additional components can be added to the solution such as carriers dissolved in the solution, diluents, etc., and **including biodegradable polymers that are co-dissolved in the**

organic solvent along with the pharmaceutical agent (see, the patent Column 7, line 49 to column 8, line 29; and especially column 8, lines 16-18).

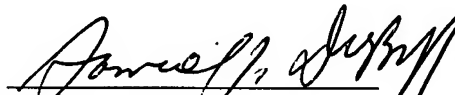
There is **no** teaching in the Lee patent as to the importance of minimizing agglomeration of coated nanoparticles by using a polymer concentration in the solution of less than about 4mg/ml as in Applicant's claimed method.

For the reasons set forth above, it is respectfully submitted that neither the Subramanian patent, the Lee patent or the Perrut publication, either individually or any combination thereof, teaches or would render obvious Applicant's claimed method in amended claim 1 and claims 23-25 dependent thereon. In view of the foregoing remarks and amendments to the claims, it is respectfully submitted that claims 23-25 are not obvious and that this rejection should be withdrawn.

Prompt action leading to an early Notice of Allowance is earnestly solicited. If the Examiner believes a telephone communication might be useful in advancing the prosecution of the application, the Examiner is invited to contact the undersigned representative of the Applicant.

Respectfully submitted,

Date: May 18, 2007


Samuel J. DuBoff
Reg. No. 25,969
Attorney for Applicants

McCARTER & ENGLISH, LLP
Financial Center, Suite A304
695 East Main Street
Stamford, CT 06901-2138
Phone: 203.399.5900
Fax: 203.399.5800



CERTIFICATE OF MAILING

I hereby certify that the enclosed Amendment is being deposited with the United States Postal Service as first class mail, postage prepaid, addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on May 18, 2007.

Dated: May 18, 2007

Patty A. Hamilton
Patty A. Hamilton